IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

WYETH, Plaintiff, v. IMPAX LABORATORIES, INC., Defendant.	Civil Action No.: 06-222 JJF **PUBLIC VERSION**

DEFENDANT IMPAX LABORATORIES, INC.'S
RESPONSIVE CLAIM CONSTRUCTION BRIEF

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I. INTRODUCTION

Since entering the market in 1994, Wyeth has reaped tens of billions of dollars from sales of venlafaxine.[1] Wyeth's monopoly is now coming to an end: its patent on venlafaxine expires at the end of the year. That is part of the bargain inherent in our patent system: a patent monopoly exists for a limited period of time. Wyeth is trying to extend that monopoly beyond its prescribed term by arguing that its new patents cover virtually any once-a-day formulation of venlafaxine. But once-a-day dosing is hardly a new idea, and Wyeth's actual invention (if any) is limited to a specific once-a-day formula.

In seeking to have its patents cover virtually any once-a-day venlafaxine, Wyeth is arguing for a claim scope that is incompatible with the express disclosures in the specification. In doing so, Wyeth also fails to adhere to any principled claim construction methodology—indeed, Wyeth's approach to claim construction is internally inconsistent:

- Wyeth seeks to construe the term "extended release formulation" broadly by disregarding the clear teachings of the specification about "the formulations of this invention," while seeking to cabin the meaning of "peaks and troughs" by reading in myriad limitations from the specification.
- Wyeth argues that "extended release formulation" should be construed to **exclude** hydrogel tablets while including all of Wyeth's other failed experiments, but in the *Teva* case, Wyeth argued that "extended release formulation" should be construed to **include** hydrogel tablets.
- Wyeth berates Impax for proposing a special definition of the term "extended release formulation," but its own proposed construction likewise departs from the ordinary meaning of that term.

[1] *See* Declaration of Courtney Towle.

Wyeth's failure to adhere to the rules of claim construction reflects Wyeth's more general failure to play by the rules. While prosecuting the patents in suit, Wyeth initially acquiesced in one examiner's rejection of Wyeth's broad method claims and agreed to narrow those claims. After Wyeth abandoned that application and filed a new application, before a different examiner, Wyeth made no mention of the first examiner's rejection, as it was required to do. Then, having shopped for a friendlier examiner in order to get the patents to issue, Wyeth shopped for a friendlier district court in order to enforce them. Wyeth made its claim construction arguments to the *Teva* court and lost. Instead of seeking reconsideration or appellate review of Judge Martini's careful and well-reasoned order, Wyeth settled with Teva and filed lawsuits against Impax and others in four different district courts.[2] Wyeth wants to brush aside the *Teva* Markman Order, arguing that it was interlocutory and, in any event, vacated. But Wyeth should not be permitted to relitigate these issues forever. The bottom line is that Judge Martini was right, and there is no basis for this Court to disagree with his conclusions.

Unlike Wyeth, Impax works within the rules. Impax's proposed constructions flow from a consistent claim construction methodology as applied by the *Teva* court. As a generic drug manufacturer, Impax relies on the bargain on which the patent system is premised—patentees are entitled to protect their inventions, but the public gets the benefit of the patent disclosure and is entitled to rely on the patentee's statements in the patent and prosecution history regarding the scope of the invention. The patent system and the Hatch-Waxman Act recognize the public benefit of generic drugs and allow for their development. Wyeth developed a once-a-day formulation of venlafaxine using particular ingredients that it characterized repeatedly as being its invention. REDACTED

[2] *See Wyeth v. Osmotica Pharm. Corp.*, No. 7:07-cv-00067 (E.D.N.C. filed Apr. 20, 2007); *Wyeth v. Lupin Ltd.*, No. 1:07-cv-00632 (D. Md. filed March 12, 2007); *Wyeth v. Anchen Pharms.*, No. 8:06-cv-386 (C.D. Cal. filed April 12, 2006).

REDACTED

Impax has not sought to market once-a-day venlafaxine while Wyeth still holds a patent on venlafaxine—that would be against the rules. But once Wyeth's patent on venlafaxine expires, Impax should be free to market its own, different once-a-day formulation of the drug.

II. REBUTTAL STATEMENT OF FACTS

Wyeth's opening brief is rife with factual assertions that find no support whatsoever in the record and thus should be disregarded.[3] We respond to Wyeth's factual assertions in order to set the record straight.

A. Once-a-day dosing is not novel

Once-a-day dosing has long been recognized as desirable, resulting in increased patient convenience, which generally leads to better dosing compliance as compared to dosing multiple times a day.[4] Motivated by the well-known convenience of once-a-day dosing, Wyeth began development of a once-a-day formulation of venlafaxine long before Effexor was even launched. Wyeth's Opening Markman Br. at 4 (hereafter "Wyeth Br."). REDACTED

[3] Wyeth, throughout its statement of facts, makes numerous factual assertions but fails to provide any supporting evidence. For example, Wyeth asserts that its clinical trials of Effexor XR resulted in the "unexpected discoveries" of better patient compliance and higher tolerance versus the immediate release formulation (Wyeth Br. at pg. 5); the therapeutic effectiveness of Effexor XR could not be assumed from the blood plasma dissolution profile (Wyeth Br. at pg. 5); the second phase of testing the prototype of Effexor XR was "extremely unpredictable"(Wyeth Br. at pg. 5). A reply brief should not serve as the opportunity for Wyeth to make such a factual record on these issues.

[4] REDACTED

Declaration of Arthur H. Kibbe, Ph.D., in Support if Defendant's Responsive Claim Construction Brief ("Kibbe Decl.") at ¶ 21.

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Wyeth initially tried to develop a once-a-day formulation using hydrogel technology,

REDACTED [8] These attempts were unsuccessful,

and Wyeth concluded that developing a hydrogel venlafaxine formulation was "impossible."[9]

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Indeed, the patent specification notes that "[w]here

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[8] *See* Ex. S at 4:60-62 ("Numerous attempts to produce extended release [venlafaxine] tablets by hydrogel technology proved to be fruitless . . . .");

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[9] Ex. S at 10:53-57.

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the production of tablets is not feasible, it is conventional in the drug industry to prepare encapsulated drug formulations which provide extended or sustained release properties."[12] The first task was to create the uncoated spheroids.

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Nonetheless, Wyeth had a hard time identifying the right combination of ingredients, and rejected certain combinations of ingredients as unworkable. In particular, the patent specification discloses that Wyeth tested polyvinylpyrrolidone

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among other ingredients, but "in the extrusion process, heat buildup occurred which dried out the extrudate so much that it was difficult to convert the extruded cylinders into spheroids.[14] Finally, Wyeth hit on a formula that resulted in stable spheroids: venlafaxine, microcrystalline cellulose (hereafter "MCC") and optionally hydroxypropylmethylcellulose (hereafter "HPMC").

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B. The dissolution profile was not the invention

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[12] Ex. S at 1:35-38.

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[14] Ex. S at 5:1-8 ("Numerous spheroid formulations were prepared using different grades of microcrystalline cellulose and hydroxypropylmethylcellulose, different ratios of venlafaxine hydrochloride and filler, different binders such as polyvinylpyrrolidone, methylcellulose, water, and polyethylene glycol of different molecular weight ranges in order to find a formulation which would provide a suitable granulation mix which could be extruded properly.")

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Table 1 of the patents-in-suit sets forth the dissolution parameters for "the formulations of this invention."[21] REDACTED

Wyeth suggests that Table 1 provides guidance as to how to develop formulations that do not contain MCC and, optionally, HPMC. Table 1 does no such thing. It provides no suggestion as to any other ingredients that might be used in such a formulation. Wyeth itself had the same basic information – target dissolution profile – when it began work on the project. Wyeth used that target dissolution profile to screen candidate formulations, but the target did not itself suggest any particular combination of ingredients that would work, which is why Wyeth experimented with a number of possible ingredients before settling on MCC and optionally HPMC. In short, Table 1 provides no guidance whatsoever as to the ingredients to be used in a successful once-a-day formulation. Nor does the patents' disclosure that one can use a mixture of more and less coated spheroids to change the dissolution profile add anything to the art; that was already known by one of ordinary skill.[23]

III. ARGUMENT

A. Extended Release Formulation is defined in the specification to include MCC and optionally HPMC

Wyeth contends that the only issue in interpreting the term "extended release formulation" is whether the intrinsic record (claims, specification, and prosecution history)

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[21] Ex. S at 6:15-21 (describing properties of the "formulations of this invention"), 6:55-64 (Table 1, setting forth "Acceptable Coated Spheroid Dissolution Rates").

REDACTED

[23] Kibbe Decl. at ¶ 14 & Exhibit 3 (citing U.S. Patent No. 2,738,303 (issued March 13, 1956)).

clearly and unmistakably demonstrates that the patentees defined the term to mean a specific formulation with a defined set of ingredients. Wyeth Br. at 13. We agree. The answer to this question is, "Yes."

Extrinsic evidence is not relevant to that analysis. Although Wyeth starts its analysis with an exhaustive review of the extrinsic evidence, Wyeth Br. at 12-14, the extrinsic evidence cannot shed light on whether the patentees gave the term "extended release formulation" a special definition. The intrinsic record is necessarily conclusive on that point.

1. Wyeth has offered no persuasive justification for this Court to depart from the *Teva* claim construction order

Wyeth offers no persuasive reason for this Court to disagree with Judge Martini's conclusion that the inventors defined the term "extended release formulation" in the specification to be a formulation with specific ingredients. The inventors repeatedly explained that "the formulations of this invention comprise" venlafaxine, MCC, and optimally HPMC.[24] All the references to "the invention" and "the formulations of this invention" in the specification refer to this formulation. The specification does not even suggest any other ingredients that might work. Indeed, the inventors were careful to note that "suitable [HPMC]s" with a low viscosity and other characteristics could be "substituted in the formulation without changing the inventive concept," but nowhere suggested that one could use altogether different ingredients.[25] Nor did the inventors ever describe a formulation comprising MCC and optionally HPMC as merely an "embodiment" of the invention—to the contrary, they were careful to distinguish between their "invention" of a formulation containing MCC and optionally HPMC and the "embodiments" of

[24] Wyeth argues that Impax's proposed construction is erroneous, in part, because it specifies "venlafaxine" and not "venlafaxine hydrochloride." Wyeth Br. at 22. To clarify, in its proposed claim construction positions, its Opening Claim Construction Brief, and this Claim Construction Response Brief, Impax uses the term "venlafaxine" to refer to "venlafaxine hydrochloride." Impax did not intend to depart from Judge Martini's claim construction, which explicitly recites venlafaxine hydrochloride.

[25] Ex. S at 4:48-50.

that invention which contained specific ratios of those ingredients.

After considering the same intrinsic evidence and the same legal principles raised here, Judge Martini rightly concluded that the inventors defined the "extended release formulation" that they invented as one comprising specific ingredients. Impax Br. at 9-10; Ex. W (*Teva* Markman Order) at 11 ("When the term 'extended release formulation' is looked at in is proper context in the specification, this Court believes that one of ordinary skill in the art would construe the term to include specific ingredients."). *See also Toro Co. v. White Consol. Indus.*, 199 F.3d 1295, 1301 (Fed. Cir. 1999) (upholding a narrow claim construction supported by the specification because claims are "not construed in a lexicographic vacuum, but in the context of the specification and drawings.").

2. There are no distinct "formulation" and "use" inventions

Wyeth tries to support a broad construction of "extended release formulation" by arguing that the specification differentiates between a "use aspect" of the invention and a "formulation" invention. Wyeth Br. at pp. 22-23. Wyeth is wrong.

a. The patents are directed to a formulation and the use of that same formulation

Instead of describing a separate "use" invention, the specification describes the uses of "the venlafaxine formulation of this invention" and "the one-a-day venlafaxine hydrochloride formulations of this invention."[26] There is no "use" invention distinct from the formulations of the invention. Indeed, the Examiner did not understand the applications to disclose distinct "use" and "formulation" inventions. Where a single application includes more than one "independent and distinct" invention, an examiner issues a restriction requirement, directing a patentee to file a distinct patent application for each invention. 35 U.S.C. § 121; MPEP §§ 201.06 and MPEP § 802.01; *see Applied Materials v. Advanced Semiconductor Materials Am.*, 98 F.3d 1563, 1577

[26] Ex. S at 2:20, 2:46-47.

(Fed. Cir. 1996). The Examiner here did not issue a restriction requirement, indicating that the Examiner did not believe there to be distinct inventions.

b. The Federal Circuit has clarified that method and formulation claims are presumed to have the same scope

In recent weeks, the Federal Circuit clarified the law of claim construction as it relates to terms used in apparatus claims and method claims in the same patent. In *Pods, Inc. v. Porta Stor, Inc*, ___ F.3d ___, 2007 WL 1226740, 82 U.S.P.Q.2d 1553 (Fed. Cir. Apr. 27, 2007) (slip opinion appears as Ex. X), the court reviewed a district court's construction of the term "carrier frame." The patent had both an apparatus claim and a method claim. Claim 1, the apparatus claim, described a "carrier frame," which the apparatus claim "specifically describe[s] as including 'right and left longitudinal elements' adjacent to 'front and rear transverse elements.'" *Pods*, slip op. at 11. Thus, the apparatus claim described "a four-sided rectangular shaped frame." *Id.* Claim 29, the method claim, described "'[a] method of lifting, handling and transporting a container on to and off from a transport vehicle'" which included "'positioning a carrier frame around the container on the transport vehicle platform.'" *Id.* at 4 (emphasis omitted). The defendant used a three-sided, U-shaped carrier frame that the parties agreed did not infringe the apparatus claim. *Id.* at 6. However, the plaintiff asserted that the defendant's use of a U-shaped carrier frame nonetheless infringed the method claim, because Claim 29 required only a "carrier frame," without describing the carrier frame's shape. *Id.* at 6-7.

The Federal Circuit held that the term "carrier frame" as used in the method claim was presumed to refer to the rectangular carrier frame described in the apparatus claim, "unless it is clear from the specification and prosecution history that the terms have different meanings at different portions of the claims." *Id.* at 12 (quoting *Fin Control Sys. Pty., Ltd. v. OAM, Inc.*, 265 F.3d 1311, 1318 (Fed. Cir. 2001)). Noting that "the only embodiments disclosed in the specification are four-sided," the court found that because "PODS has pointed to no evidence in the specification or the prosecution history that the term 'carrier frame' in claim 29 has any meaning other than the uncontested meaning in claim 1," "the term 'carrier frame' in claim 29,

as in claim 1, requires 'a four-sided or rectangular shape.'" *Id.* The Federal Circuit rejected the plaintiff's argument that "the omission in claim 29 of the detailed description of a four-sided carrier frame found in claim 1 'presumably carries consequences,'" at 7, holding instead that the method claim referred to the same carrier frame described in detail in the apparatus claim. *Id.* at 12.

Here, the patents in suit claim both a formulation and a method. Here, too, Wyeth asserts infringement only of the method claim. And the method claim uses a term – "extended release formulation" – which is used in the formulation claims and in the specification to refer to a formulation having specific properties – here, one comprised of venlafaxine hydrochloride, MCC, and, optionally, HPMC. Therefore, under the Federal Circuit's recently-announced rule, the "extended release formulation" recited in the method claims must be presumed to refer to the specific formulation set forth in the formulation claims, "unless it is clear from the specification and prosecution history that the terms have different meanings at different portions of the claims." *Id.* at 12 (quoting *Fin Control Sys.*, 265 F.3d at 1318).

Wyeth has made no showing that overcomes the presumption set forth in *Pods*. Indeed, here, as in *Pods*, the only embodiments disclosed in the specification are those described in the formulation claims. Accordingly, the term "extended release formulation" should be construed in all the claims to refer to a formulation containing venlafaxine hydrochloride, MCC, and, optionally, HPMC.

3. The patentees' express recitation that the "extended release formulations" of the invention comprise specific ingredients rebuts any presumption that claims should have different scope

Here, as in *Teva*, Wyeth argues that Impax's proposed construction renders some of the claims superfluous. Judge Martini correctly rejected that argument: claim differentiation is merely a presumption; it is not dispositive. *See, e.g., Kraft Foods, Inc. v. Int'l Trading Co.,* 203 F.3d 1362, 1368-69 (Fed. Cir. 2000) (finding the presumption of claim differentiation overcome because the specification and prosecution history narrowly described the disputed claim term);

Multiform Desiccants, Inc., v Medzam, Ltd., 133 F.3d 1473, 1480 (Fed. Cir. 1998) (rejecting application of claim differentiation because specification and prosecution history required narrow interpretation of limitation in question).

Wyeth's citation to *Pfizer* is inapposite. In *Pfizer Inc. v. Ranbaxy Labs., Ltd.*, 405 F. Supp. 2d 495, 504 (D. Del. 2005), this Court rejected a narrow construction because the specification indicated no intention to limit the independent claim. Here, however, the patentees did limit the scope of their invention and thus the scope of the claims. *See Seachange Int'l, Inc. v. C-COR Inc.*, 413 F.3d 1361, 1369 & 1375 (Fed. Cir. 2005) (narrowly construing a claim term, in light of the intrinsic evidence, resulting in two claims having the same scope); *Fantasy Sports Props. v. Sportsline.com, Inc.*, 287 F.3d 1108, 1116 (Fed. Cir. 2002) (doctrine of claim differentiation rebutted by intrinsic evidence, rendering an independent claim and two dependant claims of the same scope). The *Teva* court wrestled with the application of the doctrine of claim differentiation to this case, and correctly determined that the presumption was overcome. Ex. W (*Teva* Markman Order) at 11-12.

4. Table 1 does not support a broader invention

Wyeth makes much of the dissolution rates set forth in Table 1.

REDACTED [27] Moreover, the specification explains that "[c]onformance with the dissolution rate given in Table 1 provides the twenty-four hour therapeutic blood levels for the drug component of **the extended release capsules of this invention** in capsule form."[28] The description of Table 1 makes explicit that it relates to "the extended release capsules of this invention."[29] Thus Table 1 does not purport to set forth some broader invention; instead, it shows the acceptable dissolution ranges for the specific

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[27] REDACTED

[28] Ex. S at 6:41-45 (emphasis added).

[29] *Id.*

(encapsulated) formulations of the invention. Thus, the assertion of Wyeth's expert that Table 1 provides useful, instructive ranges for *any* dosage form – including hydrogel tables – is demonstrably wrong.[30] Instead, the relationship between in vitro dissolution and in vivo blood plasma levels depends upon the dosage form.

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5. Wyeth's proposed carve-out of hydrogel tablets does not follow from any principle of claim construction

After spending pages discussing the plain meaning of the term "extended release formulation," Wyeth does not propose that the term be construed as having its plain meaning.[31] Instead, Wyeth proposes a special definition of extended release formulation that carves out hydrogel tablets. Wyeth cannot argue that the ordinary meaning of extended release formulation excludes hydrogel tablets, because the specification explicitly recites that "extended release drug formulations are conventionally produced as compressed tablets by hydrogel table technology."[32]

[30] Kibbe Decl. at ¶ 13.

[31] Impax does not disagree with Wyeth's rendition of the plain meaning of extended release formulation. Wyeth Br. at 12. The point is that the plain meaning is not the inventors' meaning.

[32] Ex. S at 1:12-14.

Wyeth even relies on this passage to criticize Impax's proposed definition, arguing that "[s]ince claim terms are normally used consistently throughout the patent, Impax's construction of 'extended release formulation' as being limited to specific ingredients violates this rule as well." Wyeth Br. at 20. Of course, what Wyeth fails to mention is that its proposed construction of extended release formulation (which likewise excludes hydrogel tablets) is subject to exactly the same criticism.

Wyeth contends that its proposed construction was drafted "to insure that Wyeth's proposed claim construction reflects the specification's statements regarding 'hydrogel tablets.'" Wyeth Br. at 24. Presumably, Wyeth is referring to the explanation in the specification that Wyeth tried, and failed, to develop a once-a-day hydrogel formulation of venlafaxine. But Wyeth argued to Judge Martini (through these same counsel) that "extended release formulation" had its ordinary meaning and did not include any such limitation. Ex. W (*Teva* Markman Order) at 6. REDACTED

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REDACTED Wyeth has now changed its position.

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REDACTED there is a real danger in picking and choosing which limitations from the specification to read into a claim. But that is precisely what Wyeth seeks to do here by excluding hydrogel tablets, but only hydrogel tablets, from the definition of extended release formulation. And that is also why the *Teva* court's approach—grounding the definition in the inventors' consistent description of "the

invention"—was correct.

Indeed, even now, Wyeth cannot bring itself to argue that it unambiguously *disclaimed* hydrogel tablet technology. As a result, Wyeth fails to identify or follow any principle of claim construction that would support its proposed construction. Instead, Wyeth argues for the plain meaning, while conceding that the specification supports a narrower meaning because Wyeth tried and failed to make a venlafaxine hydrogel tablet. But hydrogel technology was just one of Wyeth's many failed experiments—for example, the specification explicitly teaches away from using PVP, REDACTED Indeed, neither of Wyeth's experts offers any explanation for why the definition of extended release formulation should exclude hydrogel tablets.

Wyeth's concession that "extended release formulation" cannot be given its ordinary meaning is fatal to Wyeth's claim construction position. There is nothing special about hydrogel technology that warrants excluding it, but only it, from the definition of extended release formulation. Instead, the relevant rule of claim construction is that Wyeth cannot claim more than it invented, and it did not invent anything other than the specific formulation it described in the specification as its invention.

6. The prosecution history supports Impax, not Wyeth

Wyeth offers no explanation for its conduct in first acquiescing in the examiner's rejection of its method claims and then pursuing the same claims before a second examiner without disclosing the prior rejection.[33] Instead, adopting the adage that the best defense is a good offense, Wyeth argues that the prosecution history actually supports its construction of extended release formulation. Wyeth is wrong.

First, how the examiner understood the claim scope is not dispositive as to how the claim should be construed by this Court. An examiner is required to give the claims their broadest

[33] *See Hakim v. Cannon Avent Group, PLC*, 479 F.3d 1313, 1315-16 (Fed. Cir. 2007) (adopting a narrow claim construction even when the patentee alerted the examiner to its broadening amendment).

possible construction—a construction that may be broader than the construction that is ultimately legally correct. *See, SRAM Corp. v. AD-II Eng'g, Inc.*, 465 F.3d 1351, 1359 (Fed. Cir. 2006) cert. denied, U.S. Lexis 5926 (U.S. May 21, 2007) (examiner's claim interpretation not controlling because claim construction is reviewed de novo); *Rexnord Corp. v. Laitram Corp.*, 274 F.3d 1336, 1347 (Fed. Cir. 2001) ("[W]e may presume that the examiner gave the terms in the proposed claim their 'broadest reasonable interpretation consistent with the specification,' since he was obliged to do so.").

Second, Wyeth's argument is arguably misleading. It is true that the first examiner understood that Wyeth's method claims were not directed to a specific formulation; as a consequence, the examiner rejected those claims, and Wyeth did not challenge the rejection. Wyeth argues that the second examiner had the same understanding. In support, Wyeth notes that the second examiner rejected two product claims (claims 17 and 18) that depended from a method claim (claim 14) on the basis that the method claim did not "recite any limitations describing the formulation." Wyeth Br. at 26. From this, Wyeth argues that the examiner understood that the term "extended release formulation" did not limit the formulation in the method claims. Wyeth Br. at 27, citing Ex. 12 at WYETH 002-000718. But the two preceding lines (not cited by Wyeth) are instructive: "Claims 17 and 18 recite the limitation 'the spheroids' in line 1. There is insufficient antecedent basis for this limitation in the claim." Exhibit 12 to Wyeth Br. at WYETH 002-000718. In other words, claims 17 and 18 referred to "the spheroids" but no such spheroids were disclosed in independent claim 14. Any time a dependent claim refers to "the" object, that object must be recited in the independent claim. *See Fuji Photo Film Co. v. ITC*, 386 F.3d 1095, 1100 (Fed. Cir. 2004) (patent examiner rejected proposed claim for lack of antecedent basis). In context, then, the examiner appears to have concluded that the independent claim did not recite any limitations relating to spheroids, and thus the dependent

claims were not in proper form. This has nothing to do with how the examiner understood "extended release formulation."

B. "Incidence" of nausea and emesis refers to the number of patients with nausea and emesis

Wyeth argues that the claims, specification, and its expert's declaration demonstrate that "incidence" means "degree and/or frequency." The *Teva* court considered the same argument and essentially the same evidence, and correctly rejected this argument. "Incidence" refers to the number of patients with nausea and emesis, not to the severity of the effect.

As detailed in Impax's Opening Markman Brief, the specification does not support a construction of "incidence" as including "level" or severity. Impax Br. at 17-19. Dr. Spilker has opined and compiled authority demonstrating that "incidence," as understood by one of ordinary skill in the art, does not refer to "level" or severity.[34]

According to Wyeth's expert, Dr. Hollander, extended release venlafaxine reduces both the number of patients who experience nausea and the severity of that nausea.[35] Perhaps the inventors could have claimed "diminished nausea and emesis." They didn't. Indeed, Wyeth's construction makes the word "incidence" in the claim redundant by equating "diminished nausea and emesis" with "diminished incidence of nausea and emesis." There is a presumption that the word "incidence" is there for a reason, but Wyeth reads it right out of the claim. *Ethicon Endo-Surgery v. U.S. Surgical Corp.*, 93 F.3d 1572, 1582-1583 (Fed. Cir. 1996) (recognizing that each word in the claims should be given meaning).

Wyeth argues that, because the claims are directed to a "diminished" incidence of nausea, and "diminished" can refer to either a reduction in number or a reduction in degree, "incidence"

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[34] Declaration of Bertram A. Spilker, M.D., Ph.D., F.C.P., F.F.P.M., in Support of Impax's Responsive Claim Construction Brief ("Spilker Decl.") at ¶¶ 4-9.

[35] Declaration of Eric Hollander, M.D. at 8 ("Fewer patients experience nausea with Effexor XR than with Effexor.").

likewise must refer to either a reduction in number or a reduction in degree. This is faulty logic. If the claims referred to a diminished number of trees, for example, we would not infer that the claim covered stunting the growth of trees, thereby creating "diminished trees."

Wyeth also argues that Impax's definition of "incidence" is inconsistent with the specification's disclosure that the extended release formulation "reduces by adaptation" the level of nausea and incidence of emesis that attend the administration of multiple daily dosing. But it is far from clear what that portion of the specification means. Impax's proposed construction is consistent with the idea that the body adapts to a more gradual rise in blood levels of venlafaxine with the extended release formulation of the invention, and thus fewer patients have adverse reactions at all: in other words, that adaptation reduces the number of patients who experience nausea or emesis.[36] That interpretation is further supported by the specification's earlier reference to the fact that in "the plural daily dosing regimen, the most common side effect is nausea, experienced by about forty-five percent of patients under treatment with venlafaxine hydrochloride."[37] The patent clearly refers to the number of patients suffering from side effects, not merely the severity of those effects.

Finally, in other contexts, Wyeth itself uses "incidence" to mean "the number of patients suffering from nausea and vomiting," not "degree and/or frequency." As part of the FDA approval process, Wyeth was required to submit its drug labeling to the FDA. In the "Prescribing Information" document Wyeth produced to inform doctors about the benefits and side effects of Effexor XR, Wyeth presented a table titled, "Treatment-Emergent Adverse Event ***Incidence*** in Short-Term Placebo-Controlled Effexor XR Clinical Trials in Patients With Major Depressive Disorder" (emphasis added).[38]

If Wyeth's construction of "incidence" accurately reflected the meaning of the term, one would expect the table to list results in terms of "degree and/or frequency," not in terms of a

[36] *Id.*

[37] Ex. S at 2:7-11.

[38] Spilker Decl. Ex. 7 at 28.

number of patients. But the table does just that. For each side effect listed, the table reports the percentage of test subjects taking Effexor XR who reported at least one episode of that side effect during the study. The first footnote to this table makes this clear, explaining that the table reports "Incidence, rounded to the nearest %, for events reported by at least 2% of patients treated with Effexor XR[.]"[39] Thus even Wyeth's scientists understand that "incidence" refers to the number of patients who report a side effect during a defined time period, not the severity of the side effect or the frequency with which any given patient experiences the side effect.

C. Wyeth's proposed definition of "troughs and peaks" reads in limitations that are not present in the claims

The term "troughs and peaks" has an ordinary meaning – a maximum blood plasma level and a minimum blood plasma level.[40] Wyeth does not appear to disagree with this point. Nor does Wyeth seem to disagree that this claim limitation requires that, instead of the multiple peaks and troughs associated with the immediate release form of the drug, there is one peak and one trough within a 24 hour period. Wyeth's expert Dr. Sawchuk explains:

> Because the extended release formulation of venlafaxine is administered only once a day, only one peak and one trough in venlafaxine plasma concentration are observed over a twenty-four hour interval.[41]

That is all that this claim element requires – the elimination of the multiple peaks and troughs associated with multiple doses, such that there is only one peak, and one trough, each twenty-four hours.

Wyeth proposes a construction of "[a method] for eliminating the troughs and peaks of drug concentration in a patient's blood plasma attending the therapeutic metabolism of plural daily does of venlafaxine hydrochloride" that departs from the ordinary meaning of the words in the claim. But Wyeth offers no rationale for giving these words a special definition. Indeed, Wyeth does not cite a single case in this section of its brief, nor even hint at a claim construction

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[39] *Id.* at 29 n.1.

[40] Kibbe Decl. at ¶ 30.

principle that might guide its analysis beyond simple expediency. Wyeth imports no fewer than nine separate limitations from the specification without identifying any legal principle that would justify a departure from the general rule that reading in such limitations is improper.

Wyeth did not clearly define its invention as limited to the elimination of certain kinds of peaks and troughs. But to the extent that this point is a debatable one, it is not debatable that the inventors much more clearly defined their invention as being limited to a formulation with specific ingredients. In other words, if the inventors acted as their own lexicographers with respect to this limitation, they unquestionably acted as their own lexicographers with respect to the meaning of extended release formulation as well.

Wyeth's first argument is that the claim language itself requires a peak blood level of venlafaxine between 4 to 8 hours, and "because this time to peak blood plasma level is extended, the claim language itself supports an interpretation wherein the rise and decline of blood plasma levels are flattened, *i.e.* less sharp, than the immediate release version." This is circular logic, at best. First, the fact that the claim requires a **delayed** peak in the blood plasma level hardly means that the inventors gave the word "peak" some special definition. Second, the requirement that the peak blood plasma level occur between 4 to 8 hours appears in other claims that do not have the limitation "eliminating troughs and peaks," so the requirement of a flattened peak cannot be inferred simply from that additional limitation, or else the "peaks and troughs" limitation would be mere surplusage.

Wyeth's proposed construction also may be fatally indefinite. For example, the proposed construction calls for elimination of "sharp peaks" but the claim only calls for elimination of "peaks." First, it should be almost axiomatic that "peak" should not be construed to mean "sharp peak" unless the inventors clearly so limited their invention. But, second, the proposed

[41] Declaration of Ronald J. Sawchuck, Ph.D. at 11-12.

construction gives no guidance as to how sharp is "sharp." Thus, the proposed construction goes against one of the key principles of claim construction – to clarify the claim language. *See Sulzer Textil A.G. v. Picanol N.V.*, 358 F.3d 1356, 1366 (Fed. Cir. 2004) (claim construction is meant to aid the jury); *Embrex, Inc. v. Serv. Eng'g Corp.*, 216 F.3d 1343, 1347 (Fed. Cir. 2000) ("[Claim construction] is simply a way of elaborating the normally terse claim language . . . in order to understand and explain, but not to change, the scope of the claims.").

D. Wyeth has not explained the meaning of "therapeutic metabolism"

Wyeth fails to address the meaning of "therapeutic metabolism" in its opening brief. Similarly, none of Wyeth's three experts address this term. Wyeth's expert, Dr. Sawchuck, noted that "therapeutic" means that "the blood levels experienced by a patient treated with an extended release formulation of venlafaxine hydrochloride during a 24 hour period are . . . sufficient to provide relief from the condition being treated over the course of therapy." Sawchuck Decl. at 9. But the claim does not refer to the "therapeutic metabolism" of "an extended release formulation." Instead, the claim refers to "the therapeutic metabolism of plural daily doses," referring to the immediate-release venlafaxine product (requiring more than one daily dose), not Wyeth's extended release product (requiring only a single daily dose). As a result, Dr. Sawchuk's definition of "therapeutic" has no relevance here.

As discussed in Impax's Opening Brief, this term has no meaning to a person of skill in the art, and the term is never used in the specification of the patents in suit. Impax Br. at 20. Because this term lacks meaning, it is indefinite under 35 U.S.C. § 112. Claims that are "not amenable to construction" or "insolubly ambiguous" are indefinite. *Datamize, LLC v. Plumtree Software, Inc.*, 417 F.3d 1342, 1347 (Fed. Cir. 2005). Wyeth has not presented argument or evidence to the contrary.

IV. CONCLUSION

For all the reasons set forth in Impax's Opening Markman Brief, as well as the reasons set forth above, Impax respectfully requests that the Court adopt the following constructions:

"extended release formulation" - a formulation comprising venlafaxine, MCC, and, optionally, HPMC coated with a mixture of ethyl cellulose and HPMC in an amount needed to provide a specific unit dosage administered once-a-day to provide a therapeutic blood plasma level of venlafaxine over the entire 24-hour period of administration.

"with diminished incidence(s) of nausea and emesis" - a decrease in the number of patients suffering from nausea and vomiting compared to patients receiving the same total daily dose of an immediate release formulation that is administered at least twice a day.

"for eliminating the troughs and peaks of drug concentration in a patient's blood plasma attending the therapeutic metabolism of plural daily doses of venlafaxine hydrochloride" - the peak(s) and trough(s) due to the "therapeutic metabolism" of any second or third dose given in a single day is eliminated by dosing only once every 24 hours.

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CERTIFICATE OF SERVICE

I hereby certify that on the 30th day of May 2007 I electronically filed the foregoing document, **REDACTED VERSION OF DEFENDANT IMPAX LABORATORIES, INC.'S RESPONSIVE CLAIM CONSTRUCTION BRIEF,** with the Clerk of the Court using CM/ECF which sent notification of such filing to the following:

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